REMARKS

Claims 3-13 are currently pending in the application. Only claims 3, 5 and 9 are in independent form.

Claims 3-4, 7-9, 10 and 13-16 stand rejected under 35 U.S.C. § 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Office Action states that while the specification is enabling for inhibiting the expression of TNF-α *in vitro*, it does not reasonably provide enablement for modulating, which includes enhancing and inhibiting, the expression of TNF-α *in vivo*. In order to further prosecution, the claims have been amended to specifically recite only inhibiting the expression of TNF-α, thus overcoming a portion of the present rejection.

The Office Action also states that the specification as filed does not disclose a successful *in vivo* delivery of the antisense/ribozyme compounds and that such knowledge is not currently known in the art. The Office Action states that the current state of the art teaches that the behavior of antisense oligonucleotides *in*

vivo and *in vitro* is unpredictable. However, as set forth in the attached paper by Applicants, there is disclosed that the *in vivo* use of the method as set forth in the present application does perform as indicated in the *in vitro* studies. Specifically, the attached article shows data collected by the Applicants utilizing the methods of the present invention in rats. This study shows that rats treated with the methods and compositions of the present application developed the results which were predicted based upon the *in vitro* study. Accordingly, there is sufficient support for the specification as currently pending, and reconsideration of the rejection is respectfully requested.

Claims 5-6 and 11-12 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Office Action states that there are numerous phrases in these claims which are unclear as to how they relate to the other aspects of the claim. Accordingly, in order to further prosecution, the claims have been amended to more specifically cite both what is included in the antisense oligonucleotide and how this oligonucleotide results in the regulation of TNF-α expression. Reconsideration of the rejection is respectfully requested.

Claims 13-16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Office Action states that claims 3, 13, 14 and 16 contain therein numerous phrases which lack antecedent basis. In order to further prosecution, these claims have been amended to provide sufficient antecedent basis for all phrases. Reconsideration of the rejection is respectfully requested.

Claims 15 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as being incomplete from omitting an essential step. Accordingly, in order to further prosecution, such step has been added to the claims and reconsideration of the rejection is respectfully requested.

Claim 5 stands rejected under 35 U.S.C. § 102(e) as being anticipated by the Nyce, et al patent. Reconsideration of the rejection under 35 U.S.C. § 102(e), as anticipated by the Nyce, et al patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

In Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986) it was stated: "For prior art to anticipate under §102 it has to meet every element of the claimed invention."

In Richardson v. Suzuki Motor Co., Ltd., 868 F.2d 1226, 9 U.S.P.Q.2d 1913 (Fed. Cir. 1989) it was stated: "Every element of the claimed invention must be literally present, arranged as in the claim."

The Office Action states that claim 5 reads on a synthetic nuclease resistant antisense oligonucleotide for selectively inhibiting human tumor necrosis factor alpha (TNF-α) comprising an exon targeting sequence flanking donor splice sites. The Office Action states that the claim is interpreted as reading on synthetic antisense oligodeoxynucleotides targeting intron-exon borders of human tumor necrosis factor alpha (TNF-α). However, while the Nyce, et al reference does disclose an andenosine A_1 that has an antisense molecule that may target the 5' or 3' intron-exon junctions of the adenosines A_1 receptor, the patent strictly discloses the adenosines A_1 receptor. There is no mention of targeting intron-exon junctions for other genes such as tumor necrosis factor alpha. Furthermore, this patent was filed prior to full characterization of adenosines A_1 receptor. At the time of the filing, delineation of the specific intron-exons was not completely understood. In a paper by Deckert, et al in 1995, there was disclosed further characterization of the

adenosines A_1 receptor genes. Since there is no homology between tumor necrosis factor alpha and the A_1A receptor gene and there is no similarity in function between these two sequences, there is no indication that merely the knowledge pertaining to A_1A would be useful with regard to tumor necrosis factor alpha. Accordingly, reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above, the prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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CERTIFICATE OF TRANSMISSION BY MAIL

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on April 17, 2001.

Marie M. DeWitt

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

5. (Amended) A synthetic nuclease resistant antisense oligodeoxynucleotide for selectively inhibiting human tumor necrosis factor alpha said antisense oligonucleotide comprising: an exon targeting a sequence which flanks [flanking] at least one splice [sites] site said targeting thereby regulating expression of TNF-α.

7. (Twice Amended) A pharmaceutical composition for selectively [regulating] inhibiting mammalian tumor necrosis factor alpha in a mammal in need of such treatment consisting of

an effective amount of at least one active ingredient a synthetic nuclease resistant antisense oligodeoxynucleotide having a nucleotide sequence selected from the group consisting of SEQ. ID No. 4 and SEQ. ID No. 6 in a pharmaceutically physiologically acceptable carrier or diluent.

13. (Amended) A method of selectively regulating mammalian tumor necrosis factor alpha by [the steps of] targeting for treatment [the] a tumor necrosis factor alpha splice region and then specifically modify the region to [regulate] inhibit the mammalian tumor necrosis factor alpha.

14. (Amended) The method of claim 13 further including [the step of] administering an effective amount of a synthetic nuclease resistant antisense oligodeoxynucleotide which targets exon sequences flanking donor splice sites.

15. (Amended) A method of inhibiting tumor necrosis factor alpha by targeting for treatment [the] a tumor necrosis factor alpha splice region thereby inhibiting tumor necrosis factor alpha.

16. (Amended) The method of claim 15 further including [the step of] administering an effective amount of a synthetic nuclease resistant antisense oligodeoxynucleotide which targets exon sequences flanking donor splice sites.